REMARKS/ARGUMENTS

Reconsideration of this application. Claims 1-9, 13 and 15-22 will be active in the application subsequent to entry of this amendment.

Claim amendments

In the above Claim 1 has been amended by deleting the term hydrogen for R_1 and deleting the provisos in order to overcome the issues of clarity; Claims 17 and 18 have been amended to further define the subject-matter for which protection is sought as it will be better explained in the relevant sections of this reply.

New claims 20-22 have been added to direct specific embodiments of the invention to the well-known applications in the relevant technical field.

Enablement rejection

Applicants considered the Examiner's rejection with the utmost attention, but they cannot agree with it. Applicants are not claiming "camptothecin", but substituted 7-oxime camptothecins, see specification, page 3, Summary of the invention.

That the compounds claimed herein are camptothecin derivatives cannot be disputed by any person of ordinary skill in the art.

On the other hand, that the Examiner is doubting the efficacy of the claimed compounds in treating tumors responsive to camptothecin derivatives, the Examiner's doubt will be resolved by the immense literature on "camptothecins", intended as camptothecin derivatives. A representative assay of this literature was presented in our previous reply of March 3, 2006.

In order to meet the Examiner's requirement, the claims have been amended in order to better define the invention.

Claims 17 and 18 now are directed to the treatment of tumors or viral or parasitic infections in which the tumor, the virus or the parasite are responsive to topoisomerase I inhibition. In this manner, the person skilled in the art, by simply resorting to the general common knowledge, will be able to determine which tumor, which virus or which parasite are responsive to topoisomerase I inhibition, with a simple consultation of the general literature.

New claim 20 is directed to specific tumors responding to topoisomerase I inhibition; *see* page 14, third paragraph.

New claims 20 and 21 are directed to specific applications of the invention to specific applications of the art of using camptothecins. To this end, specific support is provided by Enclosure 3 filed with the previous reply dated March 3, 2006. See in particular, but not exclusively; *see* items 14, 20, 22, 23, 24, 27, 29, 30, 35.

The discussion of the prior art provided in the specification is sufficient to establish that the claims are supported in their breadth. First, the claimed compounds are 7-oxime camptothecins and a Review published on 2004, relying on previous studies, affirmed that Gimatecan, 7-t-butoxyiminomethylcamptothecin, shows an impressive tumor efficacy in a large panel of human tumor xenografts (emphasis added); *see* Enclosure 1 filed with our reply of March 3, 2006.

The term "Gimatecan derivative" is included in the compounds of the present invention; *see* claim 4, fifth compound, and claim 5, first compound. The two compounds are disclosed in the specification in Example 3 (ST2127) and Example 4 (ST2143) for the 7-member lactone and Example 3 (ST2196), for the 5-ring member, respectively. Gimatecan is disclosed in the reference cited on page 1, third paragraph of the specification in EP 1 044 977, cited by the Examiner as its equivalent Penco et al., US 6,242,457. In this reference, two representative compounds for the general formula (I) therein disclosed are 7-t-butoxyiminomethylcamptothecin; *see* Example 2 (CPT184) and 7-t-benzyloxyiminomethylcamptothecin; *see* Example 1 (CPT172). These compounds are more potent than the clinical standard Topotecan and the closest structural reference 7-hydroxyiminomethylcamptothecin (CPT181), disclosed in US 4,399,276, cited by the Examiner; *see* Table 1. Penco et al. demonstrate the marked persistence of the antitumor activity on the ternary complex drug-DNA-topoisomerase I (Penco et al., Table 2) and the antitumor activity on a wide range of human tumor; *see* the exemplary list in Table 3.

Therefore, there is no doubt, as shown in the granted Penco et al. patent, that substituted 7-oxime derivatives of camptothecin are effective in treating tumors responsive to topoisomerase I inhibition.

Penco et al. teach that antitumor potency is enhanced by the kind of substitution at the position 7 and that the camptothecin derivatives disclosed in the patent are active in a broad range of human tumors.

It will be appreciated that ST2127, ST2143 and ST2196 are highly active compounds.

All the references cited by the Examiner, Bom et al and Bigg et al. demonstrate that the modification of the size of lactone ring of the camptothecin derivative, enhances the molecule stability, namely assures antitumor activity *in vivo*. Accordingly, the skilled person has no doubt as to the effectiveness of the claimed compounds as antitumor agents.

The claims are deemed to define the invention in a sufficiently clear manner.

The Examiner's objection about the antitumor activity of the claimed compound has no scientific basis and its withdrawal is respectfully requested.

Novelty rejection

Claim 1, has been amended by deleting the meaning of hydrogen for R_1. In this manner, the Bigg reference is definitely removed from the claims.

Obviousness rejection

- Dallavalle et al.

Applicants again maintain this citation is not available as prior art. Attached is an abstract of this paper taken from the website of the publisher. The date of June 2002 is clearly visible. In this way Applicants consider the matter be clarified. A written declaration from the publisher as to the effective publication/distribution date of this article can be obtained upon the Examiner's request.

- Penco et al. in view of Bom et al.

The Examiner's objection must be discussed in a wide horizon of argumentation, taking into account the factual inquiries that are applied for establishing a background for determining obviousness under 35 U.S.C.§ 103(a).

1. Determining the scope and contents of the prior art.

In their previous reply, Applicants explained the scope of Bom et al. and of Penco et al. Those arguments will not be repeated here but they will be relied on also in this circumstance.

Applicants explained how Bom et al. succeeded in increasing plasma stability of a campthotecin derivative by enlarging lactone ring size from 6 to 7 members, but the antitumor activity remained at least unchanged, if not lowered.

The scope of prior art as of Penco et al. is to achieve a camptothecin derivative with improved solubility, better therapeutic index, and enhanced persistence of the ternary complex

(see above). This problem is solved by providing camptothecin derivatives bearing a substituted oxime group at position 7.

The scope of prior art as of Bom et al. is to achieve a camptothecin derivative which is more stable in plasma and this goal is pursued by enlarging lactone ring from 6 to 7 members.

The scope and contents of the prior art were determined by the Examiner correctly.

2. Ascertaining the differences between the prior art and the claims at issue.

The Examiner defined correctly also the difference between Penco et al. and the claims at issue.

3. Resolving the level of ordinary skill in the art.

This crucial point was not discussed by the Examiner in the previous Office Action.

Applicants consider this lack of resolving the level of ordinary skill in the art a severe defect in the legal framework of the construction of this rejection.

In the present case, the Examiner failed in establishing an important point of law. Resolving the level of ordinary skill in the art is the crucial hinge between the prior art and the claimed subject matter, namely the invention. Construction is not trivial, but is critical in deciding patentability of claims. Applicants consider this Office Action defective from a legal point of view.

In their previous reply, Applicants explained their motivation on patentability of the claimed subject matter by discussing in detail the two references applied by the Examiner and showing in detail the benefits brought about by the present invention to the art.

In the present Office Action, the Examiner used a standard sentence to comment Applicants arguments "*Applicant's arguments have been fully considered...but they are not persuasive...*", but, Applicant's arguments were quickly dismissed in a three-line sentence with a repetition of the Examiner's interpretation of the prior art. Examiner did not comment on Applicants highlighting of the unexpected advantages of the present invention in providing camptothecin derivatives with improved plasma stability **and enhanced activity.**

In order to establish the correct legal position, Applicants respectfully ask the Examiner to reconsider the entire matter (that is, application and the prior art) and to reformulate his objection on a complete basis under the provisions of *Graham vs. John Deere Co.*

To this end, withdrawal of finality of the rejection is respectfully asked and prosecution of the examination on the basis of the claims filed in the present instance is respectfully requested.

For the sake of a streamlined prosecution, Applicants offer their interpretation of this point of law in order to demonstrate this invention is indeed patentable with respect to the prior art.

The person of ordinary skill in the art is aware of the state of the art of the subject matter disclosed in the claims and is capable of understanding the technical problem faced by the invention.

In the present circumstance, the person skilled in the art, must address the problem to enhance plasma stability of Penco et al's substituted 7-oxime camptothecin derivatives had also the problem to still enhance antitumor activity or therapeutic index (see specification on page 3, second paragraph).

The person skilled in the art would have read and understood Bom et al.'s reference and would have learned that antitumor activity of camptothecin derivatives is achieved only by inserting in position 7 of the molecule groups with a high lipophilic character, such as silyl groups. At the same time, Bom et al. teach that enlarging lactone ring to the size of 7 ring members increases plasma stability. On the other hand, the skilled person understands from the analysis of the results provided by Bom et al. that enlarging the lactone ring improves stability of the molecule in plasma, but can endanger antitumor activity.

In the frame of this teaching, the person skilled in the art has the double task to enhance plasma stability of Penco et al.'s compounds and to increase therapeutic index.

This person will consider Bom et al.'s paper and will find the teaching to enlarge lactone ring from 6 to 7 members. However, Bom et al. teach that an increase of antitumor activity is achieved by placing a group with high lipophilic character in position 7 of the camptothecin molecule. Notwithstanding the presence of the highly lipophilic substituent, enlargement of the lactone ring, albeit providing a prolonged stability in plasma, gives no substantial improvement in antitumor activity, even a worsening of antitumor activity.

The person skilled in the art in the present circumstance is a practitioner who must provide an antitumor agent, therefore, the first goal is to provide an antitumor agent endowed

with high efficacy. This person must follow the teaching of the relevant art in pursuing his tasks and goals and this person is not able to give any interpretation different than the same teaching. There is no suggestion in Bom et al. to consider separately the effects on antitumor activity of a camptothecin derivative brought by the substituent at position 7 and by enlargement of lactone ring. Bom et al. do not foresee any reasonable expectation of same or similar results when their teaching will be applied in camptothecin derivatives bearing in position 7 a substituent with a lower lipophilic degree, such as the one of Penco et al.'s substituted oximes.

The person skilled in the art need not try new paths in his technical field if there is no suggestion to do so with a reasonable expectation of success. So, there is no reason for this person to try to apply Bom et al's teaching to Penco et al.'s compounds.

The person skilled in the art, when following the prior art teaching expects to find the same results of the art and no improvements or progress is expected. This person is committed to solve a problem already present in the art and no new or further difficulties can be charged on him.

As said above, the technical problem of the present invention is to confer enhanced plasma stability to the camptothecin derivatives disclosed by Penco et al., but without compromising antitumor activity.

The present inventors were aware of the teaching of Bom et al., see the citation on page 2, ninth line from the bottom of the specification and were also aware of the risk of lowering antitumor activity and took the risk to modify their already patented compounds (Penco and Zunino are present co-inventors and co-inventors of the cited Penco et al.'s patent) into less effective antitumor agents.

The person of ordinary skill in the art cannot take any risk in performing his task and he will consider no elements of the art less than sure in their outcome and without logical link among them.

It is repeated here that Bom et al's teaching is strictly confined to camptothecin derivatives having highly lipophilic character and that plasma stability is obtained by enlarging lactone ring, but antitumor activity is barely maintained.

4. Considering objective evidence present in the application indicating obviousness or non obviousness.

In the very unlikely event this person would have gone against Bom et al.'s teaching, i.e. to try camptothecin derivatives with low lipophilic substituents and would have taken the effort to conceive new compounds and to conceive a completely new synthetic strategy (the Examiner attention's is also called on the completely different synthetic thought generated by the present inventors when compared with the synthesis proposed by Bom et al's.), this person would have been very surprised to find the claimed compounds show a very high antitumor activity, contrary to every expectation given by Bom et al.'s teaching.

Evidence is provided in the specification, see page 15, Table 1 in the specification. The high antitumor activity of the claimed compounds is totally unexpected in view of the teaching of the prior art.

Reconsideration of the present claims and withdrawal of rejection are respectfully awaited.

New grounds of rejection

Claims 1-9, 13 and 15-19 – 35 U.S.C. § 112

Amended claim 1 is filed for consideration. Formula (I) was corrected to remedy a clerical error in drawing the formula, see Applicants' remarks of March 3, 2006, point 6.

Original formula (II) is restored. Applicants regret the editing problem. Provisos have been eliminated, thus rendering the rejection moot.

In view of all the amendments herein presented and the arguments in their support, Applicants respectfully request withdrawal of all the rejections and prompt allowance of the claims of this application.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

Arthur R. Crawford
Reg. No. 25,327

ARC:eaw
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

Summary
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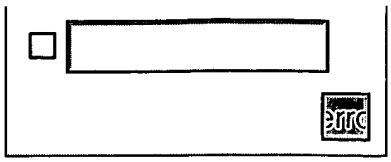
Perspectives in camptothecin development

Sergio Penco••, -Lucio Merlini••, -Franco Zunino••, -Sabrina Dallavalle••-
Sigma-Tau, Pomezia, Italy
Dipartimento di Scienze Molecolari Agroalimentari, Università di Milano, Milano, Italy
Laboratorio di Chemioterapia e Farmacologia Antitumourale Preclinica, Istituto Nazionale dei Tumori, Via Venezian 1, I 20133 Milano, Italy; Tel: +39 0223 902 267; Fax: +39 0223 902 692; , E-mail: zunino@istitutotumori.mi.it
Dipartimento di Scienze Molecolari Agroalimentari, Università di Milano, Milano, Italy

DNA topoisomerase I is recognised as a useful target for antitumour therapy. Camptothecin is the prototype topoisomerase I specific inhibitor. The impressive antitumour activity of camptothecins in preclinical models and the clinical success of topotecan and irinotecan have stimulated intense research activities and various strategies to identify novel compounds and to overcome the main limitations of the camptothecin molecule (i.e., instability of the lactone ring and reversibility of drug–target interaction). The original water-insolubility problem



of the naturally occurring compound has been overcome with the development of various water-soluble analogues, for intravenous administration. Some of these compounds fulfilled requirements for clinical development. The approaches to improve the antitumour efficacy of agents of this class rely on quite different principles. Some involve the development of prodrugs and delivery systems. Recently, novel series of lipophilic analogues have been described. These share some common features, including oral bioavailability, ability to cross the blood–brain barrier, an increased stability of the lactone ring and potent topoisomerase I inhibition. Several derivatives are still in preclinical development and some of these novel agents are presently undergoing clinical evaluation. This review will focus on the progress currently being made on various approaches in this field.

Forward Links to Citing Articles

Franco Zunino, Graziella Pratesi••. (2004) Camptothecins in clinical development. *Expert Opinion on Investigational Drugs* **13**:3, 269-284 Online publication date: 1-Mar-2004.
Summary | PDF (220 KB) | PDF Plus (280 KB)
Richard W Versace••. (2003) The silatecans, a novel class of lipophilic camptothecins. *Expert Opinion on Therapeutic Patents* **13**:6, 751-760 Online publication date: 1-Jun-2003.
Summary | PDF (153 KB) | PDF Plus (173 KB)

PDF (120 KB) PDF Plus (136 KB)

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Ashley Publications, Telephone House, 69-77 Paul Street, London, EC2A 4LQ, UK
Tel: +44 (0)20 7017 5000 · Fax: +44 (0)20 7017 7667